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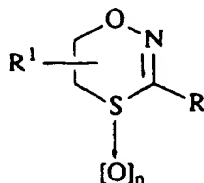
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(54) Title: ANTIBACTERIAL AND ANTIFOULING OXATHIAZINES AND THEIR OXIDES

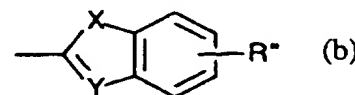
(57) Abstract

Use of 3-aryl-5,6-dihydro-1,4,2-oxathiazines and their oxides having formula (I), wherein n is 0, 1 or 2; R¹ is hydrogen, C₁₋₄alkyl or benzyl; and R represents (a) phenyl; phenyl substituted with 1 to 3 substituents independently selected from hydroxyl, halo, C₁₋₁₂alkyl, C₃₋₆cycloalkyl, trihalomethyl, phenyl, C₁₋₃alkoxy, C₁₋₃alkylthio, tetrahydropyranyloxy, phenoxy, C₁₋₄alkylcarbonyl, phenylcarbonyl, C₁₋₄alkylsulfinyl, C₁₋

4alkylsulfonyl, carboxy or its alkali metal salt, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylaminocarbonyl, phenylaminocarbonyl, tolylaminocarbonyl, morpholinocarbonyl, amino, nitro, cyano, dioxolanyl or C₁₋₄alkyloxyiminomethyl; naphthyl; pyridinyl; thienyl, preferably when n is not 2; furanyl; or thienyl or furanyl substituted with one to three substituents independently selected from C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylthio, halo, cyano, formyl, acetyl, benzoyl, nitro, C₁₋₄alkyloxycarbonyl, phenyl, phenylaminocarbonyl and C₁₋₄alkyloxyiminomethyl; or R represents a radical of formula (b) wherein X is oxygen or sulfur, Y is nitrogen, CH or C(C₁₋₄alkyloxy); and R' is hydrogen or C₁₋₄alkyl, as an antibacterial, anti-yeast, antifungal, algicidal, anti-crustacean, molluscicidal and general antifouling agent and compositions containing the same.



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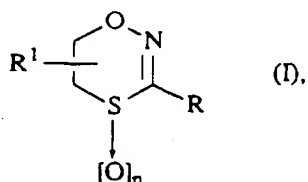
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ANTIBACTERIAL AND ANTIFOULING OXATHIAZINES
AND THEIR OXIDES

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The present invention concerns a method of controlling bacteria and fouling organisms with 3-aryl-5,6-dihydro-1,4,2-oxathiazines and their oxides, a method of protecting non-living materials other than wood, and industrial antibacterial and antifouling compositions. Surfaces of objects exposed to humid or aqueous environments are readily colonized by micro-organisms and occasionally by other, higher life forms such as molluscs and crustacea. As these organisms settle on or attach to said surfaces, the value of the exposed objects diminishes. The exterior, but possibly also the interior of the object may deteriorate, the surface changes (e.g. from smooth, clean and streamlined to rough, foul and turbulent), the weight of the object increases by the deposit of the organisms and their remnants, and the vicinity of the object may become obstructed or encumbered. The function of the object and system involved lowers and the quality of the aqueous environment deteriorates. Similar problems beset industrially used compositions such as coatings, lubricants and the like. All these phenomena are referred to as fouling. The oxathiazines of the present method and their oxides are disclosed in US-4,569,690 as herbicides, plant fungicides, plant desiccants and defoliants.

25 The present invention provides a method of controlling bacteria and fouling organisms, said method comprising applying to said bacteria or fouling organisms, or to the locus thereof an effective antibacterial or antifouling amount of a compound having the formula

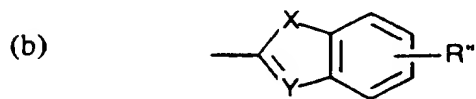


wherein n is 0, 1 or 2; R¹ is hydrogen, C₁₋₄alkyl or benzyl; and R represents (a) phenyl; phenyl substituted with 1 to 3 substituents independently selected from hydroxyl, halo, C₁₋₁₂alkyl, C₅₋₆cycloalkyl, trihalomethyl, phenyl, C₁₋₅alkoxy, C₁₋₅alkylthio, tetrahydropyranyloxy, phenoxy, C₁₋₄alkylcarbonyl, phenylcarbonyl, C₁₋₄alkylsulfinyl, C₁₋₄alkylsulfonyl, carboxy or its alkali metal salt, C₁₋₄alkyloxy-carbonyl, C₁₋₄alkylaminocarbonyl, phenylaminocarbonyl, tolylaminocarbonyl, morpholinocarbonyl, amino, nitro, cyano, dioxolanyl or C₁₋₄alkyloxyiminomethyl; naphthyl; pyridinyl; thienyl, preferably when n is not 2; furanyl; or thienyl or furanyl

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substituted with one to three substituents independently selected from C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylthio, halo, cyano, formyl, acetyl, benzoyl, nitro, C₁₋₄alkyloxy-carbonyl, phenyl, phenylaminocarbonyl and C₁₋₄alkyloxyiminomethyl; or R represents a radical of formula

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wherein X is oxygen or sulfur; Y is nitrogen, CH or C(C₁₋₄alkyloxy); and R'' is hydrogen or C₁₋₄alkyl.

10

The present invention in particular provides a method of protecting non-living materials other than wood, and the objects made of or covered by said non-living materials, against bacteria and/or fouling organisms, said method comprising applying to the surface or incorporating into said materials or objects an effective antibacterial or antifouling amount of a compound of formula (I).

15

In the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo; C₁₋₄alkyl defines straight and branch chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms comprising methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1,1-dimethylethyl, 1-methylpropyl, 2-methylpropyl; C₁₋₅alkyl includes C₁₋₄alkyl radicals as defined above and saturated hydrocarbon radicals having five carbon atoms, e.g. n-pentyl and the branched pentyl isomers; C₁₋₆alkyl includes C₁₋₅alkyl radicals as defined above and six carbon containing homologs, e.g. n-hexyl and the branched hexyl isomers. C₁₋₁₂alkyl includes C₁₋₆alkyl and saturated hydrocarbon radicals having from 7 to 12 carbon atoms, e.g. heptyl, octyl, nonyl, decyl, undecyl and their isomers. The term alkali metal cation in particular is a sodium or potassium cation. Trihalomethyl defines a methyl group being fully substituted with halo atoms, in particular trifluoromethyl and trichloromethyl. C₁₋₄alkyloxyiminomethyl defines a radical of formula -CH=N-O-C₁₋₄alkyl.

30

Particular compounds of formula (I) for use in the method are those wherein n is 0, 1 or 2; R¹ is hydrogen, C₁₋₄alkyl or benzyl; and R represents phenyl; naphthyl; pyridinyl; thienyl provided that n is not 2; furanyl optionally substituted with 1 to 3 substituents independently selected from C₁₋₄alkyl and C₂₋₅alkyloxycarbonyl; or phenyl substituted with 1 or 2 substituents independently selected from hydroxyl, halo, C₁₋₁₂alkyl, C₅₋₆cycloalkyl, trihalomethyl, phenyl, C₁₋₅alkoxy, C₁₋₅alkylthio, tetrahydropyranyloxy, phenoxy,

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C₂₋₅alkylcarbonyl, phenylcarbonyl, C₁₋₄alkylsulfinyl, C₁₋₄alkylsulfonyl, carboxy or its alkali metal salt, C₁₋₅alkoxycarbonyl, C₂₋₅alkylaminocarbonyl, phenylaminocarbonyl, tolylaminocarbonyl, morpholinocarbonyl, amino, nitro, cyano, or dioxolanyl.

5 Of interest are those compounds wherein n is 1 and R represents phenyl, thienyl or phenyl substituted with one or two substituents selected from halo and trihalomethyl; or those wherein n is 2 and R represents phenyl or phenyl substituted with one or two substituents selected from halo and trihalomethyl.

10 Of further interest are the compounds wherein R¹ is hydrogen, n is 1 or 2, and R represents phenyl, C₁₋₆alkylphenyl, halophenyl, dihalophenyl, biphenyl, C₁₋₅alkyloxyphenyl, trihalomethylphenyl, nitrophenyl, phenyl substituted with C₂₋₅alkyloxy-carbonyl, C₁₋₆alkylnitrophenyl, unsubstituted furanyl or thienyl, or furanyl or thienyl substituted with ethoxycarbonyl, cyano, chlorine or bromine.

15

Of particular interest are the compounds wherein R¹ is hydrogen, n is 1 or 2, and R represents 3-fluorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-methylphenyl, 3-ethanonephenyl, 3-nitrophenyl, 3-methyl-4-nitrophenyl or 2-thienyl.

20

Also of further interest are those compounds of formula (I) wherein R¹ is hydrogen, R is a radical of formula (b) wherein X is sulfur, Y is nitrogen or CH, and R" is hydrogen.

Preferred compounds are 5,6-dihydro-3-(2-thienyl)-1,4,2-oxathiazine, 4-oxide and
25 3-(4-chlorophenyl)-5,6-dihydro-1,4,2-oxathiazine, 4,4-dioxide.

All compounds of formula (I) can be prepared following the procedures described in US-4,569,690.

30 The compounds of formula (I) are active against gram-positive bacteria and, more importantly for use in material protection, also against gram-negative bacteria. Susceptible bacteria belong to genera such as *Aeromonas*, *Alcaligenes*, *Brevibacterium*, *Cellulomonas*, *Citrobacter*, *Corynebacterium*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Micrococcus*, *Proteus*, *Providencia*, *Pseudomonas*, *Shewanella*, *Acinobacter*, *Bacillus*,
35 *Serratia*, *Staphylococcus*, *Streptococcus* and *Xanthomonas*.

The compounds of formula (I) further are active against fouling organisms. The term "fouling organisms" is meant to comprise organisms that grow on or adhere to various

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kinds of surfaces, in particular in humid or aqueous environments such as, marine waters, fresh waters, brackish waters, rain water, and also cooling water, drainage water, waste water and sewage. Fouling organisms are Algae such as, for example, Microalgae, e.g. *Amphora*, *Achnanthes*, *Navicula*, *Amphipora*, *Melosira*, *Cocconeis*,
5 *Chlamydomonas*, *Chlorella*, *Ulothrix*, *Anabaena*, *Phaeodactylum*, *Porphyridium*;
Macroalgae, e.g. *Enteromorpha*, *Cladophora*, *Ectocarpus*, *Acrochaetium*, *Ceramium*,
Polysiphonia; Molluscs, e.g. *Mytilus*, Crustacea, e.g. *Artemia*, *Balanus*, *Elminius*
Modestus, *Verruca*, *Lepas* and Ascidia, Hydrozoa and Bryozoa.

- 10 The present invention also provides a method for the preservation of non-living materials other than wood against fungi that spoil or destroy such materials. Said method involves treating such materials with an effective fungicidal amount of a compound of formula (I).

The compounds of formula (I) are useful to protect a wide variety of non-living materials
15 other than wood, and the objects made thereof or covered thereby. Examples of non-living materials and the objects made thereof or covered thereby comprise adhesives; sizes; paper and cardboard; pulp; textiles; leather; paints; plastics, e.g. PVC and polyester; industrial compositions such as cooling media, e.g. cooling lubricants and cutting fluids, coating compositions, bath compositions (process liquids), lubricants and
20 the like; metals and alloys such as iron and steel; building materials, e.g. bricks, (paving) stones, cement and concrete; decorating materials, e.g. plaster, tiles; and any other materials that can be contaminated or destroyed by bacteria, fungi or fouling organisms.

Of particular interest are coating materials conventionally employed for decorative and
25 protective purposes. The present method is especially suited for protecting adherent coatings, whether clear or colored (i.e. comprising one or more dyes or pigments), and whether natural or synthetic, such as, for example, paints - especially antifouling paint compositions -, varnishes, lacquers, finishes, whitewash and similar coatings. The particular aptness of the present method of protecting said coating materials resides in the
30 fact that the oxathiazines employed in the method not only effectively protect the coating material in storage containers, during "in can" conservation (especially against bacteria) thus ensuring a long pot (or can) life and good storage stability, but also effectively protect the coating material and optionally its underlying substrate when it has been applied as a film to said substrate ("film" conservation). The simultaneous utility of the
35 oxathiazines for both "in can" and "film" conservation of coatings is of great practical value.

As constructions made of or covered by said non-living materials there can be mentioned

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swimming pools, baths, cooling water circulation circuits and industrial baths in various installations, e.g. in manufacturing plants or in air-conditioning installations, the function of which can be impaired by the presence and/or the multiplication of bacteria and fouling organisms. Further examples are buildings and parts of buildings such as floors, outer
5 and inner walls or ceilings, of places suffering from dampness such as cellars, bathrooms, kitchens, washing houses and the like, and which are hot-beds for bacteria and/or fouling organisms. The presence of these organisms not only is problematic from the viewpoint of hygiene and aesthetics, but also causes economic losses because said buildings and/or decorating materials deteriorate more rapidly than desired.

10

The method is especially suitable to protect underwater objects such as, for example, shiphulls, harbour installations, drying docks, sluice-gates, locks, mooring masts, buoys, drilling platforms, bridges, pipelines, fishing nets, cables and any other object in constant or frequent contact with water, by applying to said objects an antifouling
15 composition, e.g. paint composition, comprising an effective antifouling amount of a compound of formula (I).

In this context it should be noted that the present method provides a safer and ecologically more acceptable alternative for current methods using antifouling products based on heavy metals such as cuprous oxide and the like, or those based on
20 organometallic derivatives such as organo-tin compounds. The toxicity of the oxathiazines to mammals is acceptable and as such they are less hazardous for humans whether these compounds reach the human body by direct physical contact (e.g. during handling or application) or via the food chain. Their bio-degradability ensures that they are less persistent in the environment and that they cause less and shorter environmental
25 pollution and stress. The chemical stability of the oxathiazines furthermore implies that they are compatible with most non-living materials as such and do need special precautions such as the addition of agents for stabilizing the active ingredient. In materials that should form films such as lubricants, cutting fluids and coating materials, they do not impair the formation of uniform films and the practicability. In particular, in
30 coating materials they do not impair rapid curing in practical circumstances such as room temperature and outdoor conditions, and allow for strong adhesion of the composition to the substrate and /or the topcoat.

The method of application is chosen in accordance with the intended objective and the
35 prevailing circumstances. For instance, the technique used in the case of protecting lubricants, coatings or cutting fluids comprises mixing the active ingredient in said lubricants, coatings or fluids either during the manufacturing process or alternatively

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afterwards in the finished product. The active ingredient can be added in neat form or dissolved or suspended in a sufficient amount of diluent. Preferably the diluent consists of one or more of the solvents as they occur in the final composition.

- 5 The method also comprises applying compounds of formula (I), optionally in an appropriate formulation, to non-living materials by any of the techniques known in the art such as, for example, brushing, spraying, atomising, dipping, soaking, immersing, scattering and pouring. In some instances, the application may involve impregnation techniques using pressure or vacuum systems, thermal systems, injection or diffusion.

10

- Appropriate formulations are formulated following art-known procedures to emulsifiable concentrates, directly sprayable or dilutable solutions, dilute emulsions, wettable powders, soluble powders, pastes, dusts, granulates, coating compositions, e.g. paints - in particular antifouling paint compositions -, lacquers and the like. For example, the active compound can be mixed with an extender, which consists of a liquid, semi-solid or solid carrier, and optionally surface-active agents such as emulsifiers and/or dispersing agents. In coating compositions, the active compound may advantageously be incorporated in polymers, copolymers or resins. These can consist of such monomers as dialkyl (dimethyl) siloxanes, (meth)acrylic acid, (meth)acrylic acid esters, vinyl and allyl alcohols and derived esters (e.g. vinyl acetate), maleic acid, styrene, vinylchloride, butadiene, acrylamide, acrylonitrile and the like copolymerizable monomers. As resins there may be mentioned alkyd resins, polyurethanes, epoxy resins, phenolic resins and urea-formaldehyde resins. Further useful additives in said compositions comprise water-repelling agents and surface slipping agents that are capable of imparting a low surface tension of the coating film formed by the polymer or copolymer in the coating compositions.

15

- Any suitable carrier or additive that does not interfere with the antibacterial nor the antifouling activity of the active ingredient can be used in the compositions of the present invention. The solid carriers or fillers used e.g. for dusts and powders include various inert, porous and pulverous distributing agents of inorganic or organic nature such as, for example, the natural mineral fillers, e.g. calcite, talcum, kaolin, montmorillonite or attapulgite, or fillers of organic nature, e.g. powdered cork, sawdust and other fine pulverous materials. In order to improve their physical properties it can be advantageous to add highly dispersed silicic acid or highly dispersed absorbent polymers. Suitable granulated absorbent carriers are of the porous type, for example, pumice, broken brick, sepiolite or bentonite; and suitable nonsorbent carriers are materials such as calcite or

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sand. The active ingredient is mixed with these carrier substances, for example, by being ground therewith; alternatively, the inert carrier substance is impregnated with a solution of the active component in a readily volatile solvent and the solvent is thereafter removed by heating or by filtering with suction at reduced pressure. By adding wetting and/or dispersing agents, such pulverous preparations can also be made readily wettable with water, so that suspensions are obtained upon dilution.

Inert diluents used for the production of liquid preparations should preferably not be readily inflammable and should be as far as possible non-toxic to nontarget animals or plants and humans in the relevant surrounding. Diluents suitable for this purpose are, for example, water or, organic solvents such as, for example, aromatic hydrocarbons, e.g. methylbenzene, dimethylbenzene mixtures, substituted naphthalenes; alcohols and glycols and their ethers and esters, e.g. ethanol, ethylene glycol, ethylene glycol monomethyl or monoethyl ether; ketones e.g. 2-propanone, cyclohexanone and the like; strongly polar solvents; e.g. *N*-methyl-2-pyrrolidone, dimethyl sulfoxide or dimethylformamide; vegetable oils or epoxidised vegetable oils such as epoxidised coconut oil or soybean oil, and mixtures thereof. Solutions can be prepared in the usual way, if necessary, with assistance of solution promoters. Other liquid forms which can be used consist of emulsions, dispersions or suspensions of the active compound in water or suitable inert diluents, or also concentrates for preparing such emulsions, dispersions or suspensions which can be directly adjusted to the required concentration. For this purpose, the active ingredient is, for example, mixed with a dispersing, suspending or emulsifying agent. The active component can also be dissolved or dispersed in a suitable inert solvent and mixed simultaneously or subsequently with a dispersing or emulsifying agent. It is also possible to use semi-solid carrier substances of cream, ointment, paste or waxlike nature, into which the active ingredient can be incorporated, if necessary, with the aid of solution promoters and/or emulsifiers. Vaseline, petroleum wax, liquid paraffin, silicone oil and other cream-bases are examples of semi-solid carrier substances. Furthermore, it is possible for the active ingredient to be used in the form of aerosols. For this purpose the active ingredient is dissolved or dispersed in a volatile liquid suitable for use as a propellant, for example, chlorinated and/or fluorinated derivatives of methane and ethane and mixtures thereof, or compressed air. In this way solutions under pressure are obtained which, when sprayed, yield aerosols that are particularly suitable for controlling or combatting bacteria and/or fouling organisms, e.g. in closed chambers and storage rooms. For the latter purpose also smoke generators containing the active ingredient can be used.

Besides the compounds of formula (I) and the carrier, appropriate formulations often

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comprise other adjuvants conventionally employed in the art of formulation. These depend on specific applications and the user's preference. Such adjuvants are, for example, organic binding agents (e.g. chemically drying organic binder-forming polymers such as alkyd resins or physically drying organic binder-forming solids by solvent evaporation); insecticides such as, for example, chlorinated hydrocarbons, e.g. endosulfan, organophosphates, e.g. chloropyrifos, pyrethroids, e.g. permethrin and the like; additional fungicides and bactericides such as alcohols, e.g. ethanol, 2,3,3-triiodallyl alcohol; aldehydes, e.g. formaldehyde, glutaraldehyde; formaldehyde releasing compounds, e.g. 2-bromo-2-nitro-propane-1,3-diol (bronopol), 2-bromo-2-nitro-propan-1-ol; reaction products of amines and formaldehyde, e.g. triazines, 3,5-dimethyl-tetrahydro-1,3,5-2H-thiadiazine-2-thione; reaction products of amides and formaldehyde, e.g. 1-hydroxymethyl-2-thiono-1:2-dihydro-benzothiazol-N-hydroxymethylbenzothiazolinthione; phenols, e.g. 2-phenylphenol, pentachlorophenol; organic acids, e.g. propionic acid, benzoic acid, salicylic acid, naphthenic acid copper salts; inorganic acids, e.g. boric acid; amides, e.g. 2,5-dimethyl-N-cyclohexyl-N-methoxy-furan-3-carbonamide; carbamates, e.g. 3-iodopropargyl-N-butylcarbamate (IPBC), methyl-N-benzimidazol-2-ylcarbamate (Carbendazim), methyl-N-(1-butylcarbamoyl)benzimidazol-2-ylcarbamate (benomyl), zinc dimethyldithiocarbamate, zinc ethylenebisdithiocarbamate, bis-(dimethylthiocarbamoyl)disulphide; pyridine derivatives, e.g. 2-mercapto-pyridine-N-oxide, 2-chloro-6-(trichloromethyl)pyridine, 2,3,5,6-tetrachloro-4-(methylsulphonyl)pyridine, copper 8-hydroxyquinoline, 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid; azoles, e.g. tebuconazole, propiconazole, azaconazole, imazalil; heterocyclic compounds, e.g. 2-methyl-3(2H)-isothiazolone, 5-chloro-2-methyl-3(2H)-isothiazolone, 2-n-octyl-4-isothiazolin-3-one, 4,5-dichloro-2-(n-octyl)-4-isothiazolin-3-one, 1,2-benzisothiazolin-3-one, 2-methyl-4,5-trimethylene-4-isothiazolin-3-one, 2-(4-thiazolyl)-benzimidazole, 2-mercaptobenzothiazole, 2-(thiocyanomethylthio)benzthiazole; N-haloalkylthio compounds, e.g. N-trichloromethylthiophthalimide, folpet, N-trichloromethylthio-4-cyclohexane-1,2-dicarboximide, captan, N-1,1,2,2-tetrachloroethylthio-4-cyclohexene-1,2-dicarboximide, captafol, dichlofluanide, tolylfluanide; compounds with activated halogen groups, e.g. chlorothalonil; surface active agents, e.g. guanidines and biguanides; organometallic compounds, e.g. bis(tri-n-butyltin-oxide, tributyltin esters, tributyltin naphthenate, tributyltin linoleate, tributyltin benzoate, tributyltin fluoride; various compounds, e.g. pimaricine, tridemorph, methylene bistiocyanate, tolyl sulfone, dicyanobutane; metal salts, e.g. chrome-copper-arsenic; active natural products, e.g. streptomycin; auxiliary solvents such as ethylglycol acetate and methoxypropylacetate; processing additives; fixatives such as carboxymethyl-cellulose,

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polyvinyl alcohol, paraffin ; plasticizers such as benzoic acid esters and phthalates, e.g. dibutyl phthalate, dioctyl phthalate, diodecyl phthalate; UV-stabilizers or stability enhancers; dyes; color pigments; siccatives such as cobalt octoate, lead octoate and cobalt naphthenate; corrosion inhibitors; antisetling agents; anti-skinning agents such as methyl ethyl ketoxime; antifoaming agents and the like. Generally, the adjuvants are not essential to the practice of the present invention but are included in particular formulations, especially in coating formulations to optimize overall effectiveness and ease of application. They can be used therein in the conventional amounts.

The antibacterial and/or antifouling compositions which are employed in the method of the invention can contain from 0.001% to 95% of the active ingredient by weight based on the total weight of the composition. Ready-to-use compositions such as paints preferably contain from 0.5% to 20%, in particular from 1 to 10% by weight of the active ingredient. Antifouling paint compositions on the other hand can contain from 10 up to 75%, in particular from 20 to 70% of the active ingredient of formula (I) by weight based on the total weight of the dry mass of said composition (i.e. up to 50%, in particular from 5 to 25% of the active ingredient by weight based on the total weight of the antifouling composition). Preferred compositions are composed in particular of the following constituents (all percentages are by weight) :

Emulsifiable concentrates

active ingredient :	1 to 20%, preferably	5 to 10%
surfactant :	5 to 30%, preferably	10 to 20%
liquid carrier :	50 to 94%, preferably	70 to 85%

Dusts

active ingredient :	0.1 to 10%, preferably	0.1 to 1%
solid carrier :	99.9 to 90%, preferably	99.9 to 99%

Suspension concentrates

active ingredient :	5 to 75%, preferably	10 to 50%
water :	94 to 25%, preferably	88 to 30%
surfactant :	1 to 40%, preferably	2 to 30%

Granulates

active ingredient	0.5 to 30%, preferably	3 to 15%
solid carrier :	99.5 to 70%, preferably	97 to 85%

The following examples are not intended to limit, but to illustrate the scope of the

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invention.

A. Biological ExamplesExample 1 : Efficacy against Bacteria and Yeasts.

5 Test solutions were prepared by dissolving the compounds shown in Tables 1-4 in 50% ethanol and further diluting with sterile distilled water. These test solutions were pipetted into Petri dishes and mixed with warm tryptose agar to reach an active ingredient concentration of 100 ppm. After cooling, the medium was inoculated with the following yeasts or bacteria :

- 10 *Debaryomyces hansenii* (yeast) (A)
Pseudomonas alcaligenes (gram neg) (B)
Bacillus cereus mycoides (gram pos) (C)
Pseudomonas aeruginosa (gram neg) (D)
Flavobacterium sp. (gram neg) (E)
15 *Streptomyces albus* (gram pos) (F)
Enterobacter aerogenes (gram neg) (G)
Escherichia coli (gram neg) (H)

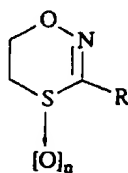
20 After sufficient growth of the untreated cultures, the compounds were evaluated using the following rating system :

0 = growth equal to control.

1 = inhibition of growth by the compound.

25 2 = no growth under the influence of the compound.

The scores measured for antibacterial and antifouling efficacy of the compounds of this invention are listed in Tables 1-4. The sign '-' signifies the compound was not tested.

Table 1

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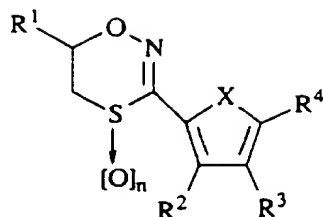
Compounds			Bacteria							
Co. no.	n	R	A	B	C	D	E	F	G	H
1	1	4-chlorophenyl	2	1	2	0	2	2	0	2
2	2	2,4-dichlorophenyl	2	0	2	0	2	0	0	0
3	1	3-nitrophenyl	2	2	2	1	2	2	1	2

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Compounds			Bacteria							
4	1	3,4-dichlorophenyl	2	1	2	0	2	2	0	2
5	2	2-methylphenyl	2	0	2	0	2	2	0	1
6	1	3-fluorophenyl	2	1	2	0	2	2	0	2
7	1	2-furanyl	2	1	2	0	2	0	0	0
8	1	2-thienyl	2	2	2	1	2	2	2	2
9	1	3-methoxyphenyl	0	0	0	0	0	0	0	0
10	1	4-methylphenyl	2	1	2	1	2	2	0	2
11	2	4-methylphenyl	2	1	1	1	2	1	0	0
12	2	2-furanyl	0	0	0	0	0	0	0	0
13	1	3-trifluoromethyl phenyl	2	0	2	0	2	2	0	2
14	1	4-ethanonephenyl	2	1	2	1	2	2	0	2
15	1	2,6-dichlorophenyl	1	0	1	0	0	0	0	0
16	2	2,6-dichlorophenyl	2	0	2	0	0	0	0	0
17	2	phenyl	0	0	0	0	0	0	0	0
18	2	4-chlorophenyl	-	1	2	0	2	2	0	0
19	2	3,5-dichlorophenyl	-	0	2	0	2	2	0	0
20	1	4-butoxyphenyl	0	0	0	0	0	0	0	0
21	1	3,5-dichlorophenyl	-	2	2	0	2	2	0	0
22	1	4-benzoic acid ethyl ester	-	1	0	0	2	2	0	0
23	2	3-chlorophenyl	0	0	0	0	0	0	0	0
24	2	4-trifluoromethyl phenyl	-	0	2	0	2	2	2	0
25	1	4-trifluoromethyl phenyl	-	1	2	0	2	2	0	0
26	1	3-benzoic acid, methyl ester	-	0	2	0	2	2	0	0
27	2	3-bromophenyl	-	1	2	0	2	2	0	2
28	1	4-ethoxyphenyl	-	0	0	0	2	2	0	0

-12-

Table 2

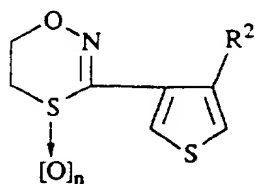


Co. No.	R ¹	R ²	R ³	R ⁴	X	n	M.P. (° C)
29	H	H	H	CO ₂ CH ₃	O	0	85-89
30	H	H	H	CO ₂ CH ₃	O	2	126-129
31	H	H	H	CO ₂ CH ₃	O	1	118-119
32	H	CH ₃	H	H	S	0	oil
33	H	CH ₃	H	H	S	1	73-75
34	H	H	H	H	S	2	99-101
35	H	H	H	Br	S	0	82-83
36	H	H	H	Br	S	1	113-114
37	H	CH ₃	H	H	S	2	60-62
38	H	H	H	Br	S	2	118-119
39	H	H	CO ₂ CH ₃	CH ₃	O	0	87-88
40	H	H	Br	H	S	0	74-75
41	H	H	Br	H	S	1	169-173
42	H	H	Br	H	S	2	126-127
43	H	H	CO ₂ CH ₃	CH ₃	O	2	156-157
44	H	H	CO ₂ CH ₃	CH ₃	O	1	147-148
45	H	H	CH ₃	CO ₂ CH ₃	S	1	150-152
46	H	H	CH ₃	CO ₂ CH ₃	S	2	125-126
47	H	H	H	CH ₃	S	0	62-63
48	H	H	H	CH ₃	S	1	109-111
49	H	H	H	CH ₃	S	2	101-102
50	CH ₃	H	H	H	S	1	114-115
51	CH ₃	H	H	H	S	2	147-148
52	CH ₃	H	H	H	S	0	70-72
53	H	H	H	CO ₂ CH ₂ CH ₃	S	0	68-69
54	H	H	H	CO ₂ CH ₂ CH ₃	S	1	109-110
55	H	H	H	CO ₂ CH ₂ CH ₃	S	2	123-124
56	H	H	H	CN	S	0	136-137
57	H	H	H	CN	S	1	160-162

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Co. No.	R ¹	R ²	R ³	R ⁴	X	n	M.P. (° C)
58	H	H	H	CN	S	2	153-155
59	H	H	H	Cl	S	0	74-77
60	H	H	H	Cl	S	1	102
61	H	H	H	Cl	S	2	113-114
62	H	H	H	CHO	S	0	48-49
63	H	H	H	NO ₂	S	0	162-163
64	H	H	H	NO ₂	S	1	186-188
65	H	H	H	NO ₂	S	2	160-161
66	H	H	H	CH=NOCH ₃	S	2	168-170
67	H	H	H	C ₆ H ₅	S	0	100-103
68	H	H	H	C ₆ H ₅	S	1	144-147
69	H	H	H	C ₆ H ₅	S	2	95-98
70	H	H	NO ₂	C ₆ H ₅	S	0	140-145
71	H	H	CH ₃	Br	S	0	oil
72	H	H	CH ₃	Br	S	1	100-104
73	H	H	Br	CH ₃	S	0	64-67
74	H	H	COOH	CH ₃	O	0	
75	H	H	CONHC ₆ H ₅	CH ₃	O	0	
76	H	H	CONHC ₆ H ₅	CH ₃	O	0	
77	H	H	CONHC ₆ H ₅	CH ₃	O	0	

Table 2a

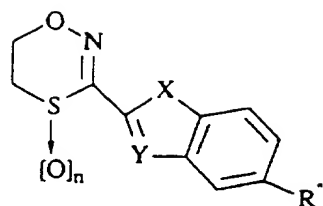


5

Co. No.	R ²	n	M.P. (° C)
78	H	2	102-104
79	H	1	106-107

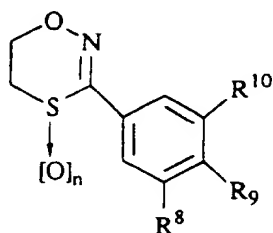
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Table 3



Co. No.	R''	X	Y	n	M.P.(°C)
80	H	O	N	2	255
81	H	O	N	1	190-191
82	H	O	N	0	143-144
83	H	S	N	2	226-227
84	H	S	N	0	150-151
85	H	S	N	1	192-195
86	H	S	CH	0	132-134
87	H	S	CH	1	140-142
88	H	S	CH	2	150-154
89	CH ₃	O	N	1	209-210
90	CH ₃	O	N	2	215-216
91	H	S	C-OCH(CH ₃) ₂	1	oil

5 Table 4



Co. No.	R ⁸	R ⁹	R ¹⁰	n	M.P.(°C)
92	H	F	H	2	136-138
93	H	F	H	1	132-133
94	F	F	H	2	106-108
95	F	F	H	1	128-130
96	F	F	H	0	63-65
97	CF ₃	H	CF ₃	1	110-113
98	CF ₃	H	CF ₃	0	44-48
99	CF ₃	H	CF ₃	2	76-78
100	F	H	F	0	103-104

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Co. No.	R ⁸	R ⁹	R ¹⁰	n	M.P.(°C)
101	F	H	F	2	108-110
102	F	H	F	1	138-139
103	CO ₂ CH(CH ₃) ₂	Cl	H	0	oil
104	CO ₂ CH(CH ₃) ₂	Cl	H	1	127-129
105	CO ₂ CH(CH ₃) ₂	Cl	H	2	82-83
106	H	CH=NOCH ₃	H	1	85-87
107	H	CH=NOCH ₃	H	2	104-106

Example 2 : Efficacy against Fresh-water algae

- 9 ml of Bold's algal broth containing an appropriate concentration of test compound, was inoculated in a 5.5 cm diameter plastic Petri dish with 1 ml of a two week old stock culture of one of three species of green algae (*Chlamydomonas dysosmos*, *Chlorella vulgaris* or *Ulothrix confervicola*) or the blue-green bacterium *Anabaena cylindrica*. The dishes were incubated in a climate room under a photosynthetically active radiation level of 40 $\mu\text{mole.m}^{-2}.\text{sec}^{-1}$ at 20°C during the day (16 h) and 18°C at night (8 h). Evaluation was performed after 14 days by visually estimating the percentage of algal growth as compared to controls. Results are expressed as minimum test concentration (in ppm) giving 90% mortality.

Compounds			Concentration (ppm)			
Co. no.	n	R	Chlamydomonas dysosmos	Chlorella vulgaris	Ulothrix confervicola	Anabaena cylindrica
4	1	3,4-dichlorophenyl	2.5	10	2.5	2.5
8	1	2-thienyl	2.5	5	1	2.5
18	2	4-chlorophenyl	2.5	10	5	2.5
19	2	3,5-dichlorophenyl	5	10	2.5	2.5
21	1	3,5-dichlorophenyl	1	5	1	2.5
25	1	4-trifluoromethyl phenyl	2.5	10	2.5	5

Example 3 : Efficacy against Marine algae

9 ml of Provasoli ASP-2 (Artificial Seawater-2) medium containing an appropriate concentration of test compound, was inoculated in a 5.5 cm diameter plastic Petri dish with 1 ml of a two weeks old stock culture of the diatom *Phaeodactylum tricornutum* or the unicellular red alga *Porphyridium* sp. The dishes were incubated in a climate room

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under a photosynthetically active radiation level of $40 \mu\text{mole.m}^{-2}.\text{sec}^{-1}$ at 20°C during the day (16 h) and 18°C at night (8 h). Evaluation was performed after 14 days by visually estimating the percentage of algal growth as compared to controls.

Compounds 1, 2, 3, 4, 5, 14, 15, 16, 18, 19, 21, 25, 27 caused 90% mortality at concentration levels equal to or lower than 1 ppm.

Example 4 : Efficacy against *Artemia*

Into 1 ml of artificial sea-water containing different amounts of the test compound, approximately 15 *Artemia* Instar II larvae were added. After 24 hours of static incubation with continuous illumination the test was evaluated.

Compounds 2, 4, 5, 11, 13, 18, 19 caused 100% mortality at concentration levels equal to or lower than 10 ppm.

B. Composition examples (all percentages are by weight)

Example 5 : Composition examples for solid compounds of formula (I)

a) Emulsifiable concentrates : emulsions of any concentration could be obtained from these concentrates by dilution with water.

	a)	b)
compound of formula (I)	10%	1%
octylphenol polyethylene glycol ether (4-5 moles of ethylene oxide)	3%	3%
calcium dodecylbenzenesulfonate	3%	3%
castor oil polyglycol ether (36 moles of ethylene oxide)	4%	4%
cyclohexanone	30%	10%
dimethylbenzene mixture	50%	79%

b) Dusts : were obtained by mixing the active ingredient with the carriers, and grinding the mixture in a suitable mill.

	a)	b)
compound of formula (I)	0.1%	1%
talcum	99.9%	-
kaolin	-	99%

c) Suspension concentrates from which suspensions of any desired concentration could be obtained by dilution with water were obtained by intimately mixing finely ground active ingredient with the adjuvants.

	a)	b)
compound of formula (I)	40%	5%
ethylene glycol	10%	10%
nonylphenol polyethylene glycol ether		

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	(15 moles of ethylene oxide)	6%	1%
	sodium lignosulfate	10%	5%
	carboxymethylcellulose	1%	1%
	37% aqueous formaldehyde solution	0.2%	0.2%
5	silicone oil in the form of a 75% aqueous emulsion	0.8%	0.8%
	water	32%	77%

Example 6 : Composition examples for liquid active ingredients of formula (I)

- 10 a) Emulsifiable concentrates : emulsions of any concentration could be obtained from these concentrates by dilution with water.

		a)	b)	c)
	compound of formula (I)	20%	40%	50%
	calcium dodecylbenzenesulfonate	5%	8%	5.8%
15	castor oil polyethylene glycol ether (36 moles of ethylene oxide)	5%	-	-
	tributylphenol polyethylene glycol ether (30 moles of ethylene oxide)	-	12%	4.2%
	cyclohexanone	-	15%	20%
20	dimethylbenzene mixture	70%	25%	20%

- b) Solutions suitable for application in the form of microdrops.

		a)	b)	c)	d)
	compounds of formula (I)	80%	10%	5%	95%
25	ethylene glycol monoethyl ether	20%	-	-	-
	polyethylene glycol (MG 400)	-	70%	-	-
	<u>N</u> -methyl-2-pyrrolidone	-	20%	-	-
	epoxidised coconut oil	-	-	1%	5%
	petroleum distillate (boiling range				
30	160-190°C)	-	-	94%	-

- c) Granulates : prepared by dissolving the active ingredient in dichloromethane, spraying the solution onto the carrier, and subsequently evaporating the solvent.

		a)	b)
35	compound of formula (I)	5%	10%
	kaolin	94%	-
	highly dispersed silicic acid	1%	-
	attapulgate	-	90%

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d) Dusts : were obtained by intimately mixing the carriers with the active ingredient.

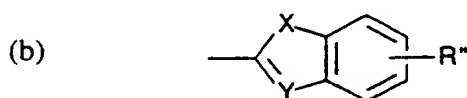
	a)	b)
compound of formula (I)	2%	5%
5 highly dispersed silicic acid	1%	5%
talcum	97%	-
kaolin	-	90%

Example 7 : Composition examples for paints

10	a)	Compound of formula (I)	6.0 %
		Titanium dioxide	17.1 %
		Whiting	9.7 %
		Talc	13.2 %
		Calgon	0.1 %
15		Hydroxyethylcellulose (3% solution in water)	12.5 %
		Co-solvent	1.2 %
		Minor additives	0.4 %
		Water	27.7 %
20		Vinyl acetate/versatate copolymer emulsion	12.1 %
	b)	Compound of formula (I)	1.0 %
		Titanium dioxide	26.4 %
		Soya alkyd resin	44.0 %
25		White spirit	27.5 %
		Cobalt octoate (8%)	0.3 %
		Lead octoate (33%)	0.7 %
		Methyl ethyl ketoxime	0.1 %

- $$\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{R}^1 - \text{C} - \text{N} \\ \diagdown \quad \diagup \\ \text{S} - \text{C} - \text{R} \\ | \\ [\text{O}]_n \end{array} \quad (I)$$

(a) phenyl; phenyl substituted with 1 to 3 substituents independently selected from hydroxyl, halo, C₁₋₁₂alkyl, C₅₋₆cycloalkyl, trihalomethyl, phenyl, C₁₋₅alkoxy, C₁₋₅alkylthio, tetrahydropyran-yloxy, phenoxy, C₁₋₄alkylcarbonyl, phenylcarbonyl, C₁₋₄alkylsulfinyl, C₁₋₄alkylsulfonyl, carboxy or its alkali metal salt, C₁₋₄alkyloxy-carbonyl, C₁₋₄alkylaminocarbonyl, phenylaminocarbonyl, tolylaminocarbonyl, morpholinocarbonyl, amino, nitro, cyano, dioxolanyl or C₁₋₄alkyloxyiminomethyl; naphthyl; pyridinyl; thienyl, preferably when n is not 2; furanyl; or thienyl or furanyl substituted with one to three substituents independently selected from C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylthio, halo, cyano, formyl, acetyl, benzoyl, nitro, C₁₋₄alkyl-oxycarbonyl, phenyl, phenylaminocarbonyl and C₁₋₄alkyloxyiminomethyl; or R represents a radical of formula



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- BNSDOCID: <WO 9505739A1 ! >

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oxathiazine, 4,4-dioxide.

4. A method according to claim 2 wherein the non-living material is an adherent coating material such as paint, antifouling paint, varnish, lacquer, finish or whitewash.
- 5 5. A method according to claim 4 wherein the adherent coating material is conserved in a storage container or wherein the coating material has been applied as a film to a substrate.
- 10 6. A method according to claim 2 for protecting underwater objects such as shiphulls, harbour installations, drying docks, sluice-gates, locks, mooring masts, buoys, drilling platforms, bridges, pipelines, fishing nets, cables and any other object in constant or frequent contact with water, by applying to said objects an antifouling composition comprising an effective antifouling amount of a compound of formula (I) as defined in claim 1.
- 15 7. A method according to claim 2, wherein the amount of the compound of formula (I) ranges from 0.001% to 95 % by weight based on the total weight of the composition.
- 20 8. A coating composition comprising
 - (a) as active ingredient a compound of formula (I) as defined in claim 1, and
 - (b) polymers or copolymers derived from such monomers as dialkyl siloxanes, (meth)acrylic acid, (meth)acrylic acid esters, vinyl and allyl alcohols and derived esters, maleic acid, styrene, vinylchloride, butadiene, acrylamide, acrylonitrile, or
- 25 resins such as alkyd resins, polyurethanes, epoxy resins, phenolic resins and urea-formaldehyde resins.
9. A coating composition according to claim 8 further comprising one or more additives selected from the group consisting of water-repelling agents; surface slipping agents;
- 30 organic binding agents; insecticides; fungicides ; bactericides; auxiliary solvents; processing additives; fixatives; plasticizers ; UV-stabilizers or stability enhancers; dyes; color pigments; siccatives; corrosion inhibitors; antisetling agents; anti-skinning agents ; and antifoaming agents.
- 35 10. An antifouling paint composition according to claim 8 comprising from 10% up to 75% by weight of the active ingredient based on the total weight of the dry mass of said antifouling paint composition.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/02784A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A01N43/88

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 104 940 (UNIROYAL) 4 April 1984 & US,A,4 569 690 (ID) cited in the application -----	

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

3 November 1994

Date of mailing of the international search report

16. 11. 94

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP 94/02784

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0104940	04-04-84	AU-B- 544881	20-06-85
		AU-A- 1961883	05-04-84
		CA-A- 1273921	11-09-90
		GB-A, B 2127817	18-04-84
		JP-A- 59080670	10-05-84
		US-A- 4569690	11-02-86
		US-A- 4675044	23-06-87

US-A-4569690	11-02-86	AU-B- 544881	20-06-85
		AU-A- 1961883	05-04-84
		CA-A- 1273921	11-09-90
		EP-A- 0104940	04-04-84
		GB-A, B 2127817	18-04-84
		JP-A- 59080670	10-05-84
		US-A- 4675044	23-06-87
